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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,086	10/08/2003	Hans-Peter Hohmann	20606 US (C038435/0111674	7182

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Stephen M. Haracz
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104-3300

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 03/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/681,086	HOHMANN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 23-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 23-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 08 October 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/12/04 & 4/5/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In the preliminary amendment filed October 8, 2003, an amended abstract has been submitted, claims 1-22 and 33-40 have been cancelled. Therefore, claims 23-32 are examined.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because non-initialed and/or non-dated alterations have been made to the address of inventor, Hans-Peter Hohmann. See 37 CFR 1.52(c).

Abstract

3. The abstract of the disclosure filed October 8, 2003 does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 23-32 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a process for decoupling production of a specific target fermentation product (i.e., riboflavin) from biomass production in a fermentation medium comprising: (a) providing a recombinantly produced microorganism that contains a polynucleotide sequence which encodes biosynthetic enzymes for a target fermentation product (i.e., riboflavin), and (b)

introducing a biotin auxotrophy into the microorganism to control biomass production by limiting the concentration of a substrate complementing the auxotrophy in the fermentation medium; and a microorganism made by the process, wherein the microorganism is a riboflavin production microorganism RB50 containing multiple copies of pRF69 and transformed with the polynucleotide sequence of SEQ ID NO:1, does not reasonably provide enablement for a process for decoupling production of a target fermentation product from biomass production in a fermentation medium comprising: (a) providing a recombinantly produced microorganism that contains a polynucleotide sequence which encodes biosynthetic enzymes for a target fermentation product, and (b) introducing an auxotrophy into the microorganism to control biomass production by limiting the concentration of a substrate complementing the auxotrophy in the fermentation medium; and a microorganism made by the process, where the structures of recombinantly produced microorganisms, target fermentation products and auxotrophy-causing polynucleotides are not identified. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 23-32 are directed to a process for decoupling production of a target fermentation product from biomass production in a fermentation medium; and a microorganism made by the process. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides a process for decoupling production of a target fermentation product from biomass production in a fermentation medium. This process includes providing a recombinantly produced microorganism that has been engineered to contain a polynucleotide sequence which encodes the biosynthetic enzymes for a target

fermentation product, where the maximal production of the target fermentation product is dependent on an unlimited supply of a target fermentation product substrate for the microorganism. Next, an auxotrophy is introduced into the microorganism to control biomass production by limiting the concentration of a substrate complementing the auxotrophy in the fermentation medium; and a fermentation production microorganism made by the process. There are no indicia that the present application enables the full scope of the claims in view of the claimed method as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding recombinantly produced microorganisms, target fermentation products and auxotrophy-causing polynucleotides, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification describes introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO:1 into a riboflavin production microorganism RB50 containing multiple copies of pRF69, culturing fermentations, and measuring biomass and riboflavin production at

different biotin concentrations (see Examples 1-3). However, the specification has not identified various recombinantly produced microorganisms that contain biosynthetic enzymes for produce target fermentation product and various auxotrophy-causing polynucleotides, and their use in the claimed method.

(3). The state of the prior art and relative skill of those in the art:

The related art (references on pages 1-4 of the specification) teach recombinant production of riboflavin and genes involved in the riboflavin biosynthetic pathways; and the art contains many examples of required genes whose mutation is likely to cause auxotrophy (e.g., Dev et al. (1984), cited in IDS). However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on identification of various target fermentation products, various recombinantly produced microorganisms transformed with various auxotrophy-causing polynucleotides, and the use of these recombinantly produced microorganisms in the claimed method.

(4). Predictability or unpredictability of the art:

The claims encompass a process for decoupling production of a target fermentation product from biomass production in a fermentation medium; and a microorganism made by the process. The art contains many examples of required genes whose mutation is likely to cause auxotrophy, however, not all biosynthetic pathways for all compounds required for growth of host cells are known in the art. The genes must first identified before they can be mutated, and the number of possible mutations is virtually endless, thus the sequences of auxotrophy-causing genes are unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a process for decoupling production of a target fermentation product from biomass production in a fermentation medium; and a microorganism made by the process. The specification describes introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO:1 into a riboflavin production microorganism RB50 containing multiple copies of pRF69, culturing fermentations, and measuring biomass and riboflavin production at different biotin concentrations (see Examples 1-3). However, the specification has not identified various recombinantly produced microorganisms that contain biosynthetic enzymes for producing target fermentation product and various auxotrophy-causing polynucleotides, and their use in the claimed method. Moreover, there are no working examples demonstrating the use of various recombinantly produced microorganisms transformed with various auxotrophy-causing polynucleotides. Since the specification does not provide sufficient teachings on identification of various recombinantly produced microorganisms that contain biosynthetic enzymes for producing target fermentation product and various auxotrophy-causing polynucleotides, and their use in the claimed method, it is necessary to carry out further undue experimentation to identify the recombinantly produced microorganisms transformed with various auxotrophy-causing polynucleotides, and to assess the effect of these microorganisms in the claimed method.

(6). Nature of the Invention

The scope of the claim encompasses a process for decoupling production of a target fermentation product from biomass production in a fermentation medium; and a microorganism made by the process, but the specification does not provide sufficient teachings on the identities

of various recombinantly produced microorganisms that contain biosynthetic enzymes for producing target fermentation product and various auxotrophy-causing polynucleotides, and their use in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed method associated with variants, the teachings in the specification are limited, and the sequences of auxotrophy-causing polynucleotides are unpredictable, and therefore, it is necessary to carry out further undue experimentation to identify the functional variants.

5. Claims 23-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 23-32 are directed to a process for decoupling production of a target fermentation product from biomass production in a fermentation medium comprising: (a) providing a recombinantly produced microorganism that contains a polynucleotide sequence which encodes biosynthetic enzymes for a target fermentation product, and (b) introducing an auxotrophy into the microorganism to control biomass production by limiting the concentration of a substrate complementing the auxotrophy in the fermentation medium (claims 23-31); and a microorganism made by the process (claim 32). While the specification indicates that the invention provides a process for decoupling production of a target fermentation product from biomass production in a fermentation medium by introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO:1 into *bacillus subtilis* RB50 containing multiple copies of the engineered *rib*

operon pRF69, culturing fermentations, and measuring biomass and riboflavin production at different biotin concentrations, which shows the product yield (i.e., the amount of riboflavin produced on the consumed glucose) is 33% higher in the decoupled process to the coupled process (see Examples 1-3), the specification does not disclose a genus of variants for target fermentation products, recombinantly produced microorganisms that contain a polynucleotide sequence which encodes biosynthetic enzymes for a target fermentation product, and auxotrophy-causing polynucleotides. A single working example (culturing RB50::[pRF69]Bio$^-$ transformed with SEQ ID NO:1 at different biotin concentration to produce riboflavin; Example 3) does not provide written description for the genus of variants in the claimed method. Furthermore, the specification does not disclose various mutations in the auxotrophy-causing polynucleotide sequences. Without guidance on structures of recombinantly produced microorganisms, target fermentation products and auxotrophy-causing polynucleotides, as well as structure to function/activity for auxotrophy-causing polynucleotides, one skilled in the art would not know how to identify the functional variants used in the claimed method. The lack of description on the structures of recombinantly produced microorganisms, target fermentation products and auxotrophy-causing polynucleotides, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claim 32 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U. S. Patent 6,656,721. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 32 in the instant application discloses a microorganism made by a process for decoupling production of a target fermentation product from biomass production in a fermentation medium comprising: (a) providing a recombinantly produced microorganism that contains a polynucleotide sequence which encodes biosynthetic enzymes for a target fermentation product, and (b) introducing an auxotrophy into the microorganism to control biomass production by limiting the concentration of a substrate complementing the auxotrophy in the fermentation medium, wherein the step (b) can comprise introducing a polynucleotide sequence comprising SEQ ID NO:1 into the microorganism; and the specification discloses the microorganism can be a riboflavin production microorganism RB50 containing multiple copies of the engineered *rib* operon pRF69 (see Example 1, page 20, lines 2-4) . This is obvious variation in view of claim 9 in the patent which discloses a riboflavin production microorganism RB50 containing multiple copies of pRF69, where the microorganism is transformed with the polynucleotide sequence of SEQ ID NO:1. Both sets of claims are directed a riboflavin production microorganism RB50 containing multiple copies of pRF69, where the microorganism is transformed with the polynucleotide sequence of

SEQ ID NO:1. Thus, claim 32 in the present application and claim 9 in the patent are obvious variations of a riboflavin production microorganism RB50 containing multiple copies of pRF69, where the microorganism is transformed with the polynucleotide sequence of SEQ ID NO:1.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
March 13, 2006